Diovan®/Diovan HCT® Clinical Summary for Formulary Review

Please consult complete Prescribing Information

Diovan® (valsartan) is a nonpeptide, orally active and specific angiotensin II antagonist acting on the AT_1 receptor subtype. Diovan HCT® is a combination of valsartan and hydrochlorothiazide (a diuretic). Diovan® and Diovan HCT® are indicated for the treatment of hypertension. Diovan HCT® is not for initial therapy. Diovan may be used alone or in combination with other antihypertensive agents. Diovan® is also indicated for the treatment of heart failure (NYHA class II-IV). In a controlled clinical trial, Diovan® significantly reduced hospitalizations for heart failure. There is no evidence that Diovan® provides added benefit when it is used with an adequate dose of an ACE inhibitor. In clinically stable patients with left ventricular failure or left ventricular dysfunction following a myocardial infarction, Diovan® is indicated to reduce cardiovascular mortality.[1]

Pk data	$t_{1/2}$	Peak Effect	AT_1:AT_2 Receptor Affinity	Bioavailability
Valsartan	6 hours	2-4 hours	20,000:1	25%

Diovan®/Diovan HCT® : HYPERTENSION

- **General Hypertension:**

Comparator	Efficacy	Note:
Amlodipine 5mg[2]	Equal	Diovan 80mg compared with amlodipine 5mg had less peripheral edema.
Lisinopril 10mg[3]	Equal	Diovan 80mg compared with Lisinopril 10mg had lower incidence of cough.
Enalapril 20mg[4]	Equal	Diovan 80mg compared with Enalapril 20mg had lower incidence of cough, and Diovan showed better response rates.
Atenolol 50mg[5]	Equal	Diovan 80mg compared with Atenolol 50mg had better tolerability.
24-hour BP efficacy		
Diovan 80/160/320 mg[6]	Dose dependent	Demonstrated 24 hour dose dependent BP control through out the dosing range.
Diovan 160 mg[7]	Equal QAM or QPM	Diovan provides 24 hour BP control independent of time of administration.
Combination with HCTZ		
Diovan HCT[8]	Improved	Diovan HCT provided improved BP control in patents not adequately controlled on Diovan monotherapy.

- **Special Patient Populations:**

Population	Design	Results	Notes
Pediatric Hypertension	Patients 6-16 years old with hypertension treated w/ Valsartan or Placebo	Dose levels of valsartan (low, medium and high) significantly reduced systolic blood pressure by -8, -10, -12 mm Hg from baseline	Valsartan was effective and well tolerated in hypertensive patients age 6-16 years old
Elderly Systolic Hypertension[9]	Patients > 65 w/ Systolic Hypertension treated w/ Valsartan or Placebo	SBP reductions of 19.2 mmHg vs 8.8 mmHg (p=<0.001) at 8 weeks	Valsartan was effective and well tolerated in the elderly for systolic hypertension
Isolated Systolic Hypertension (ISH)[10]	Patients w/ ISH treated w/ Valsartan or Amlodipine +/- HCTZ	SBP efficacy was similar between the 2 groups w/ better tolerability w/ Valsartan	Valsartan alone or w/ HCTZ showed similar efficacy and less incidence of edema with valsartan-based vs. Amlodipine-based
African Americans (AA)[11]	AA patients w/ mild to mod HTN treated w/ Valsartan/ HCTZ or Amlodipine	SBP efficacy was similar between the 2 groups w/ a lower incidence of joint swelling and edema w/ Valsartan/HCTZ	Valsartan/HCTZ as effective as amlodipine in AA's with mild to mod hypertension w/ less incidence of joint swelling and edema

Diovan®: HEART FAILURE and POST MYOCARDIAL INFARCTION

- **Heart Failure: ValHeFT** [1,12]
  - Diovan® is also indicated for the treatment of heart failure (NYHA class II-IV). In a controlled clinical trial, Diovan significantly reduced hospitalizations for heart failure. There is no evidence that Diovan provides added benefit when it is used with an adequate dose of an ACE inhibitor.
  - Reduced overall HF morbidity by 13% (p=0.009)
  - Reduced first heart failure hospitalization by 27.5% (p<0.00001)
  - In patients not receiving ACEI:
    i. Reduction in all-cause mortality by 41% (p=0.017)
    ii. Reduction in HF morbidity by 49% (p=0.0002)
    iii. Reduction in HF hospitalization by 57% (p=0.0006)
- **Post-MI: VALIANT** [1,13]
  - Diovan is indicated to reduce CV mortality in clinically stable post-MI patients with LV failure or LV dysfunction
  - No difference in overall mortality in the three treatment groups
  - Non-inferirity analysis showed it is unlikely that Diovan has less than about half of the estimated effect of captopril, clearly demonstrating an effect of Diovan. There were no added benefits when Diovan was added to captopril.

Important Considerations :

When used in pregnancy, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. When pregnancy is detected,DIOVAN or DIOVAN HCT should be discontinued as soon as possible. See **WARNINGS: Fetal/Neonatal Morbidity and Mortality** in the prescribing information.

DIOVAN and DIOVAN HCT are contraindicated in patients who are hypersensitive to any component of these products. Because of the thiazide component, DIOVAN HCT is contraindicated in patients with anuria or hypersensitivity to sulfonamide-derived drugs.

Volume and or salt depletion should be corrected in patients prior to administering DIOVAN or DIOVAN HCT or symptomatic hypotension may occur.

Care should be exercised with dosing of DIOVAN in patients with severe renal impairment. As a consequence of inhibiting the renin-angiotensin system, changes in renal function may be observed in susceptible individuals (e.g. patients with renal artery stenosis or severe heart failure).

In hypertension, the most common AEs: headache and dizziness. The most common AEs in HF: dizziness, hypotension and diarrhea. In post-MI, the most common AEs resulting in drug discontinuation: hypotension, cough, increased serum creatinine and rash.

No significant differences between adverse events, DIOVAN or DIOVAN HCT and placebo. AEs more frequent with DIOVAN than placebo: viral infection (3% vs 2%), fatigue (2% vs 1%), abdominal pain (2% vs 1%); the most common AEs: headache and dizziness. An increase in dizziness was observed with the 320 mg (8%) vs 10 mg to 160 mg (2% to 4%). AEs more frequent with DIOVAN HCT than placebo: nasopharyngitis (2.4% vs 1.9%). In individual studies, a dose-related increase in the incidence of dizziness was observed in DIOVAN HCT-treated patients.

No relevant differences were identified between the adverse experience profile for pediatric patients aged 6-16 years and that previously reported for adult patients. Diovan is not recommended for treatment of children below the age of 6 years or children of any age with a glomerular filtration rate <30 mL/min/1.73 m^2, as no data are available

The antihypertensive effect of Diovan is independent of age, gender or race. However, antihypertensive drugs that affect the RAAS have generally been found to be less effective in low-renin hypertensives (frequently blacks) than in high-renin hypertensives (frequently whites).

DIOVAN and DIOVAN HCT are indicated for the treatment of hypertension. DIOVAN HCT is not indicated for the treatment of HF or post MI. DIOVAN HCT is for patients who need even more than DIOVAN or HCTZ alone and is not indicated for initial therapy.

Diovan® is available as tablets containing valsartan 40mg, 80mg,160mg or 320mg.
Diovan HCT® is available as tablets containing valsartan/hydrochlorothiazide 80/12.5mg, 160/12.5mg, 160/25mg, 320/12.5mg and 320/25mg.

References

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